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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,500	07/24/2006	Roderick H. Scott	ABLE-0027	9312

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EXAMINER	
ARIANI, KADE	
ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/561,500	SCOTT ET AL.	
	Examiner	Art Unit	
	KADE ARIANI	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on April 14, 2009, has been received and entered.

Claims 30-36 and 60-63 have been cancelled.

Claims 37-59 are pending in this application and were examined on their merits.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/14/2009 has been entered.

Applicant's arguments with respect to claims 37-59 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 39 the word "substantially" in the recitation "between substantially 1 to 2mM" is confusing and therefore renders the claim indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 30-34 under 35 U.S.C. 102(b) as being anticipated by Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226), is withdrawn due to applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 30-40, and 60-63 under 35 U.S.C. 103(a) as being unpatentable over Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226), is withdrawn due to Applicant's amendments to the claims.

The rejection of claims 41-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woude et al. (in IDS, PNAS, 1997, Vol. 94, p.1160-1165) in view of Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226), is withdrawn due to applicant's amendments to the claims.

The rejection of claims 50-59 are rejected are rejected under 35 U.S.C. 103(a) as being unpatentable over Woude et al. (PNAS, 1997, Vol. 94, p.1160-1165) and Arendt et al. (Neuroscience, 1998, Vol. 85, No.4, p.1337-1340) in view of Ballard C.G. (European Neurology, 2002, Vol. 47, p.64-70) and further in view of Bunc et al. (Toxicon, 2002, Vol. 40, p.843-849), is withdrawn due to applicant's amendments to the claims.

Claims 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226) in view of Woude et al. (in IDS, PNAS, 1997, Vol. 94, p.1160-1165).

Claims 37-40 are drawn to a method for the reversible formation of membrane pores, the method comprising the steps, of : a) incubating the membrane in the presence of a composition comprising a reversible pore-forming sponge toxin, comprising at least one polymeric 1,3-alkylpyridinium salt (ply-APS); and b) removing

the composition from contact with the cell, the method further comprising addition of zinc solution (to attenuate the reversible formation of membrane pore), wherein the concentration of zinc solution is between 1 to 2 mM, and wherein the concentration of zinc solution is 1.5 mM.

Malovrh et al. teach a method for the reversible formation of membrane pores (inhibiting pore formation during hemolysis), the method comprising the steps of, incubating the membrane in the presence of a composition comprising a reversible pore-forming sponge toxin, comprising at least one polymeric 1,3-alkylpyridinium salt (ply-APS) (p.222 1st column 1st and 2nd paragraphs). Malovrh et al. teach that poly-APS induced pore formation/hemolysis is reversible, it can be inhibited by adding Zn2+, at 1mM concentration, and restored by the addition of EDTA (p.224, 1st column 1st paragraph lines 2-5).

Malovrh et al. do not teach removing the composition from contact with the cell. However, a person of ordinary skill in the art at the time the invention was made would have been able to remove the composition from contact with the membrane by known methods, including, centrifuging the membranes, washing the membrane or replacing the composition with the standard media (p.1162 1st column 3rd paragraph lines 3-4).

Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to apply the teachings of Woude et al. and to remove the composition from contact with the membrane in the method as taught by Malovrh et al. to provide a method for the reversible formation of membrane pores, because Woude et

al. teach removing the composition from contact with the cells to measure the extent of hemolysis at different time intervals.

Claims 41-49 are rejected Woude et al. (in IDS, PNAS, 1997, Vol. 94, p.1160-1165) in view of Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226) and further in view of Saito et al. (Gene Therapy, Jan. 2003, Vol. 10, p.72-78).

Claims 41-49 are drawn to a method for transfection of a macromolecule into a cell *in vitro*, the method comprising the steps of: a) incubating the cell in the presence of a composition comprising a reversible pore-forming sponge toxin, comprising at least one polymeric 1,3-alkylpyridinium salt (ply-APS); b) removing the composition from contact with the cell; and c) adding a macromolecule, the macromolecule is cDNA, the cell is incubated in the presence of the composition for 5 minutes, prior to the addition of the macromolecule, the composition and macromolecules are removed and replaced with standard media, cells are incubated for 180 minute.

Woude et al. teach a method for transfection of a macromolecule into a cell *in vitro*, comprising the steps of: a) incubating the cell in the presence of a composition comprising a pyridinium compound, removing the composition from contact with the cell, adding a macromolecule, the macromolecule is cDNA, 1 µg DNA was used, prior to the addition of the macromolecule, the composition and macromolecules are removed and replaced with standard media (Abstract and p.1161, 2nd column 5th paragraph). Woude et al. further teach that the pyridinium compound induced hemolysis (pore formation) is

the mechanism involved in the DNA delivery by the pyridinium compound (p.1163 2nd column 3rd paragraph lines 1-5, 8-10, and 13-14).

Woude et al. do not teach poly-APS, the cell is incubated in the presence of the composition for 5 minutes, 2.5 µg nucleic acid, and cells are incubated for 180 minute. However, Malovrh et al. teach a composition comprising a reversible pore-forming sponge toxin, comprising at least one polymeric 1,3-alkylpyridinium salt (ply-APS) (p.222 1st column 1st and 2nd paragraphs). Malovrh et al. the cells were incubated in the presence of the composition for above 250 seconds =4.1 minutes (p.223 2nd column Figure 3 Y-axis of the graph, data point for poly-APS corresponds to between 250 and 300 seconds).

Further motivation is in Saito et al. who teach using pore-forming agents with hemolytic activity as an enhanced gene delivery system is advantageous over other delivery systems, since they are capable of delivering larger sized particles (p.73 1st column 1-19). Saito et al. teach transfection wherein the cells are incubated for 4 hours with a reversible pore forming agent (p.81 2nd column 3rd paragraph lines 20-22).

Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to try and to use a composition comprising poly-APS as taught by Malovrh et al. in the transfection method of Woude et al. according to the teachings of Malovrh et al. and Saito et al. with a reasonable expectation of success, in order to provide a method for transfection of a macromolecule into a cell *in vitro*, because Malovrh et al. teach reversible pore-formation and hemolysis by poly-APS, and in Saito et al. teach using pore-forming agents with hemolytic activity for enhanced gene

delivery is advantageous over other delivery systems. Moreover, the selection of the concentration of nucleic acid to be added and the incubation time in the transfection method would have been a routine matter of optimization to a person of ordinary skill in the art at the time the invention was made, because Woude et al. teach adding 1 µg nucleic acid, and because Saito et al. teach incubating cells with the reversible pore forming agent for 4 hours during transfection.

Claims 50-53 are rejected are rejected under 35 U.S.C. 103(a) as being unpatentable Woude et al. (in IDS, PNAS, 1997, Vol. 94, p.1160-1165) and Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226) and further in view of Arendt et al. (Neuroscience, 1998, Vol. 85, No.4, p.1337-1340) and further in view of Saito et al. (Gene Therapy, Jan. 2003, Vol. 10, p.72-78).

Claims 50-53 are drawn to a method for transfection of a macromolecule into a cell *in vivo*, the method comprising the steps of: a) incubating the cell in the presence of a composition comprising a reversible pore-forming sponge toxin, comprising at least one polymeric 1,3-alkylpyridinium salt (ply-APS) and a macromolecule, the macromolecule is the cytoskeletal protein tau, and hippocampal neurone.

As mentioned immediately above, Woude et al. teach a method for transfection of a macromolecule into a cell *in vitro*.

Woude et al. do not teach a composition comprising at least poly-APS, the macromolecule is protein tau, and hippocampal neurone. However, Malovrh et al. teach sponge toxin poly-APS. However, Malovrh et al. teach a composition comprising a

reversible pore-forming sponge toxin, comprising at least one polymeric 1,3-alkylpyridinium salt (ply-APS) (p.222 1st column 1st and 2nd paragraphs).

Saito et al. teach using reversible pore-forming agents with hemolytic activity for delivering large sized particles and macromolecules (p.73 1st paragraph lines 1-19).

Arendt et al. teach an *in vivo* method of studying a neurological disease comprising injecting okadaic acid to the cerebral cortex of a rodent (*in vivo*) (p.1337, 2nd column, p.1338, 1st column and Fig.1.). Arendt et al. further teach hyperphosphorylated protein tau from Alzheimer's disease (AD) brains (p.1337, 2nd column 3rd paragraph). Arendt et al. teach transgenic animal models of Alzheimer disease, and to produce a Ad-like tau pathology *in vivo* (p. 1337 Introduction 1st column 1st paragraph lines 1-5, and 2nd column 2nd paragraph lines 5-6).

Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to combine the prior art teachings and to try to apply the method as taught by Woude et al. in the presence of poly-APS, to transfect the hippocampal neurones with protein tau *in vivo*, according to teachings of Malovrh et al. and Saito et al. and Arendt et al. in order to provide a method for transfection of a macromolecule into a cell *in vivo*. The motivation as taught by Arendt et al. would be to provide a transgenic animal model with Ad-like tau pathology.

Claims 54-59 are rejected are rejected under 35 U.S.C. 103(a) as being unpatentable over Arendt et al. (Neuroscience, 1998, Vol. 85, No.4, p.1337-1340) in

view of Bunc et al. (Toxicon, 2002, Vol. 40, p.843-849) and further in view of Ballard C.G. (European Neurology, 2002, Vol. 47, p.64-70).

Claims 54-59 are drawn to a rodent model and a method of studying a neurological disease comprising applying a composition comprising a reversible pore-forming sponge toxin, comprising at least one polymeric 1,3-alkylpyridinium salt (ply-APS), tau protein, and phosphatase inhibitor, to the hippocampus of a rodent, the phosphatase inhibitor is okadaic acid.

Arendt et al. teach a rodent model and a method of studying a neurological disease comprising applying okadaic acid to the cerebral cortex of a rodent (p.1337, 2nd column, p.1338, 1st column and Fig.1.). Arendt et al. further teach one major abnormalities in AD are made up by the microtubule-associated protein tau in a hyperphosphorylated form (p.1337, 1st column). Arendt et al. also teach okadaic acid applied into rat brain induce a hyperphosphorylated state of tau at some of those sites that are found to be hyperphosphorylated in tau preparation obtained from Alzheimer's disease (AD) brains (p.1337, 2nd column 3rd paragraph).

Arendt et al. do not teach applying a composition comprising at least poly-APS. However, Bunc et al. teach poly-APS is a potent acetylcholinesterase inhibitor, and the acetylcholinesterase inhibitory effects are not responsible for the lethal activity of the toxin (Abstract and p.847, 1st column lines 2-5).

Further motivation is in, Ballard who teaches therapeutic approaches in the treatment of Alzheimer's disease (AD) were developed with the aim of enhancing

cholinergic function, the most successful of which has been the use of cholinesterase inhibitors (Abstract tan dp.65, 1st column 2nd paragraph).

Therefore, a person of ordinary skill in the art at the time the invention was made knowing the acetylcholinesterase inhibitory effects of poly-APS, and the success of cholinesterase inhibitors in the treatment of Alzheimer's disease (AD), would have been motivated to modify the method of Arendt et al. by applying a composition comprising at least poly-APS, according to the teachings of Bunc et al. to provide a rodent model and a method of studying a neurological disease with a reasonable expectation of success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kade Ariani whose telephone number is (571) 272-6083. The examiner can normally be reached on 9:00 am to 5:30 pm EST Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kade Ariani
Examiner
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